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(71) Applicants *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE). **DAINIPPON SUMITOMO PHARMA CO. LTD.** [JP/JP]; 6-8, Dosho-machi 2-chome, Chuo-ku, Osaka-shi, Osaka (JP).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MCINALLY, Thomas** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **THOM, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **WADA, Hiroki** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; Astrazeneca AB, S-SE-151 85 Södertälje (SE).

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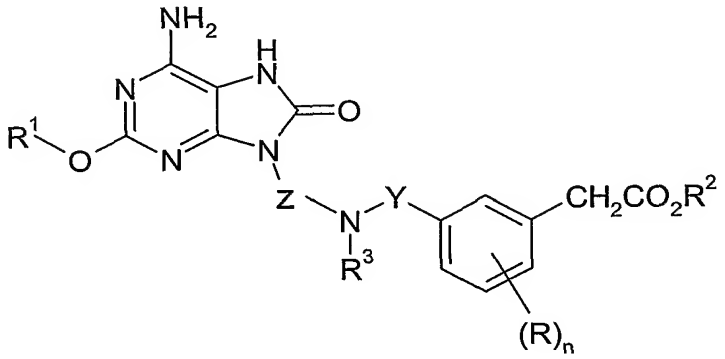
(54) Title: PURINE DERIVATIVES HAVING IMMUNO-MODULATING PROPERTIES



(I)

(57) Abstract: The present invention provides compounds of formula (I) wherein n, Y, Z, R, R^1, R^2 and R^3 are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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PURINE DERIVATIVES HAVING IMMUNO-MODULATING PROPERTIES

The present invention relates to adenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

The immune system is comprised of innate and acquired immunity, both of which work cooperatively to protect the host from microbial infections. It has been shown that innate immunity can recognize conserved pathogen-associated molecular patterns through toll-like receptors (TLRs) expressed on the cell surface of immune cells. Recognition of invading pathogens then triggers cytokine production (including interferon alpha(IFNα)) and upregulation of co-stimulatory molecules on phagocytes, leading to modulation of T cell function. Thus, innate immunity is closely linked to acquired immunity and can influence the development and regulation of an acquired response.

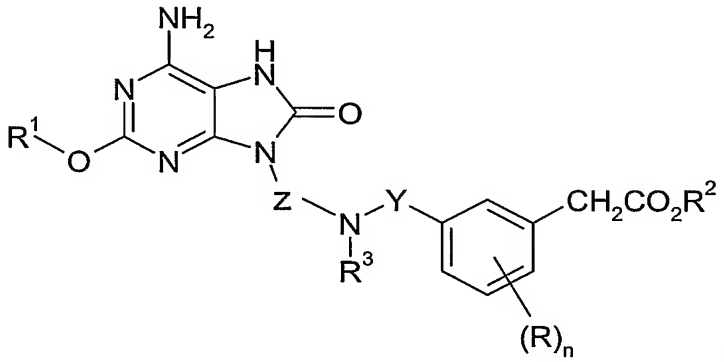
TLRs are a family of type I transmembrane receptors characterized by an NH_2-terminal extracellular leucine-rich repeat domain (LRR) and a COOH-terminal intracellular tail containing a conserved region called the Toll/IL-1 receptor (TIR) homology domain. The extracellular domain contains a varying number of LRR, which are thought to be involved in ligand binding. Eleven TLRs have been described to date in humans and mice. They differ from each other in ligand specificities, expression patterns, and in the target genes they can induce.

Ligands which act via TLRs (also known as immune response modifiers (IRMS)) have been developed, for example, the imidazoquinoline derivatives described in US Patent No. 4689338 which include the product Imiquimod for treating genital warts, and the adenine derivatives described in WO 98/01448 and WO 99/28321.

International Patent Application No. PCT/JP2005/005401 describes a class of 9-substituted-8-oxoadenine compounds having immuno-modulating properties which act via TLR7 that are useful in the treatment of viral or allergic diseases and cancers.

It has now surprisingly been found that a subset of the compounds generically disclosed in International Patent Application No. PCT/JP2005/005401 possess properties such as increased aqueous solubility which makes them particularly suitable for use in inhalation therapy. Without being bound to any particular theory, it is believed that the increased solubility of the compounds (in the lung) results in increased potency, leading to a reduction in the dose required for efficacy. This in turn improves the safety margins of the compounds.

In accordance with the present invention, there is therefore provided a compound of formula



(I)

wherein

R^1 represents a C_1-C_6 alkyl group;

Z represents a C_2-C_6 alkylene group;

Y represents a C_1-C_3 alkylene group;

R^2 represents a C_1-C_6 alkyl group;

n is an integer from 0 to 2;

each group R independently represents halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_1-C_3 haloalkyl;

R^3 represents $-(CH_2)_m$-NR^4R^5;

m is an integer from 2 to 6;

either R^4 and R^5 each independently represent hydrogen or C_1-C_6 alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring optionally comprising a further ring hetero group NR^6; and

R^6 represents hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

In the context of the present specification, unless otherwise stated, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Examples of C_1-C_6 alkyl groups/moieties include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. Similarly, an alkylene group may be linear or branched. Examples of C_1-C_6 alkylene groups include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene and 1-, 2- or 3-ethylpropylene. A C_1-C_3 haloalkyl substituent group will comprise at least one halogen atom, e.g. one, two, three, four or five halogen atoms, examples of which include trifluoromethyl or pentafluoroethyl. When R^4 and R^5 together represent a 3- to 8-membered saturated heterocyclic ring, it should be understood that the ring will contain no more than two ring hetero moieties: the nitrogen ring atom to which R^4 and R^5 are attached and optionally a group NR^6.

R^1 represents a C_1-C_6, or C_1-C_5, or C_1-C_4, or C_1-C_3, or C_1-C_2 alkyl group.

In an embodiment of the invention, R^1 represents a C_1-C_4 alkyl group, for example, an n-butyl group.

Z represents a C_2-C_6 alkylene group, for example, a C_2-C_4 or C_3-C_4 alkylene group.

In an embodiment of the invention, Z represents a linear C_2-C_4 or C_3-C_4 alkylene group such as ethylene, n-propylene or n-butylene.

Y represents a C_1-C_3 alkylene group such as methylene, ethylene or n-propylene.

R^2 represents a C_1-C_6, or C_1-C_5, or C_1-C_4, or C_1-C_3, or C_1-C_2 alkyl group.

In an embodiment of the invention, R^2 represents a C_1-C_2 alkyl group, for example, a methyl group.

n is an integer 0, 1 or 2.

In an embodiment of the invention, n represents 0.

Each group R independently represents halogen (such as fluorine, chlorine, bromine or iodine), C_1-C_3 alkyl (such as methyl, ethyl or n-propyl), C_1-C_3 alkoxy (such as methoxy, ethoxy or n-propoxy), or C_1-C_3 haloalkyl (such as dibromomethyl, dichloromethyl, bromochloromethyl, trifluoromethyl or pentafluoroethyl).

In an embodiment of the invention, n is 1 or 2 and each group R represents a halogen atom, e.g. fluorine.

R^3 represents $-(CH_2)_m$-NR^4R^5 where m is an integer 2, 3, 4, 5 or 6.

In an embodiment of the invention, m is 2 or 3.

In an embodiment of the invention, R^4 and R^5 each independently represent hydrogen or C_1-C_6, or C_1-C_5, or C_1-C_4, or C_1-C_3, or C_1-C_2 alkyl.

In one embodiment, R^4 and R^5 each independently represent hydrogen or methyl.

In an alternative embodiment, R^4 and R^5 together with the nitrogen atom to which they are attached form a 3-, 4-, 5-, 6-, 7- or 8-membered, e.g. 5- to 6-membered, saturated heterocyclic ring optionally comprising a further ring hetero group NR^6 where R^6 represents hydrogen or C_1-C_6, or C_1-C_5, or C_1-C_4, or C_1-C_3, or C_1-C_2 alkyl. Examples of heterocyclic rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl and 4-methylpiperazin-1-yl.

In an embodiment of the invention,

R^1 represents n-butyl;

Z represents n-propylene $(CH_2)_3$) or n-butylene ($(CH_2)_4$);

Y represents methylene;

R^2 represents methyl;

n is 0;

R^3 represents $-(CH_2)_m$-NR^4R^5;

m is 2 or 3;

either R^4 and R^5 each independently represent hydrogen or methyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring optionally comprising a further ring hetero group NR^6; and

R^6 represents methyl.

Examples of compounds of the invention include:

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(dimethylamino)propyl]amino}methyl)phenyl]acetate,

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-pyrrolidin-1-ylpropyl)amino]methyl}phenyl)acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][2-(dimethylamino)ethyl]amino}methyl)phenyl]acetate,

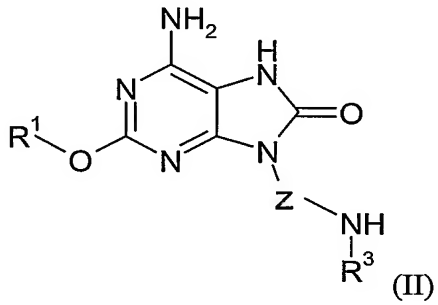
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylamino)propyl]amino}methyl)phenyl]acetate,

Methyl [3-({[4-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)butyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate,

and pharmaceutically acceptable salts of any one thereof.

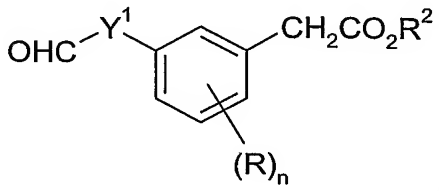
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

(a) reacting a compound of formula



(II)

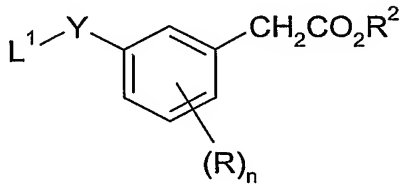
wherein Z, R^1 and R^3 are as defined in formula (I), with a compound of formula



(III)

wherein Y^1 represents a bond or C_1-C_2 alkylene group and n, R and R^2 are as defined in formula (I) in the presence of a suitable reducing agent (e.g. sodium triacetoxyborohydride); or

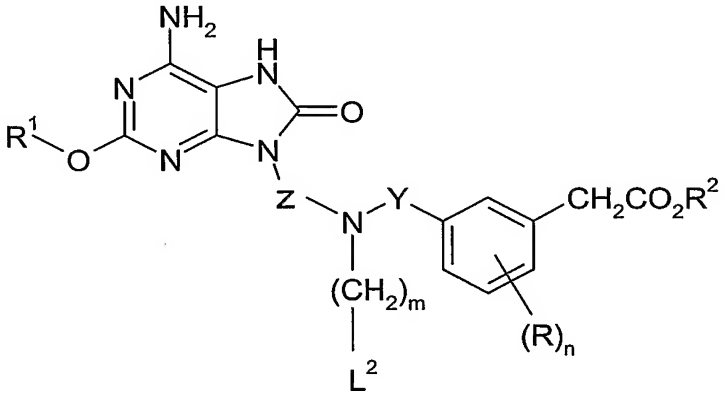
(b) reacting a compound of formula (II) as defined in (a) above with a compound of formula



(IV)

wherein L^1 represents a leaving group (e.g. halogen, mesylate or triflate) and n, Y, R and R^2 are as defined in formula (I) in the presence of a suitable base (e.g. sodium carbonate or potassium carbonate); or

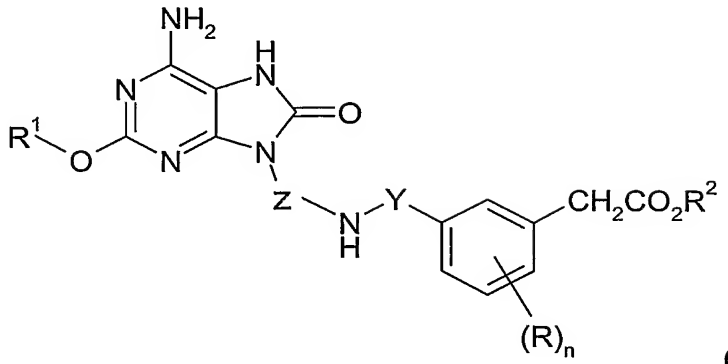
(c) reacting a compound of formula



(V)

wherein L^2 represents a leaving group (e.g. halogen, mesylate or triflate) and m, n, Y, Z, R, R^1 and R^2 are as defined in formula (I), with a compound of formula (VI), HNR^4R^5, wherein R^4 and R^5 are as defined in formula (I); or

(d) reacting a compound of formula



(VII)

wherein n, Y, Z, R, R^1 and R^2 are as defined in formula (I), with a compound of formula

$$L^3\text{-}(CH_2)_m\text{-}NR^4R^5 \quad \text{(VIII)}$$

wherein L^3 represents a leaving group (e.g. halogen, mesylate or triflate) and m, R^4 and R^5 are as defined in formula (I); or

(e) reacting a compound of formula (VII) as defined in (d) above with a compound of formula

$$OHC\text{-}(CH_2)_{m-1}\text{-}NR^4R^5 \quad \text{(IX)}$$

wherein m, R^4 and R^5 are as defined in formula (I) in the presence of a suitable reducing agent (e.g. sodium triacetoxyborohydride);

and optionally after (a), (b), (c), (d) or (e) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

In process (a), the reaction may conveniently be carried out in an organic solvent such as 1-methyl-2-pyrrolidinone, 1,2-dichloroethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 150°C.

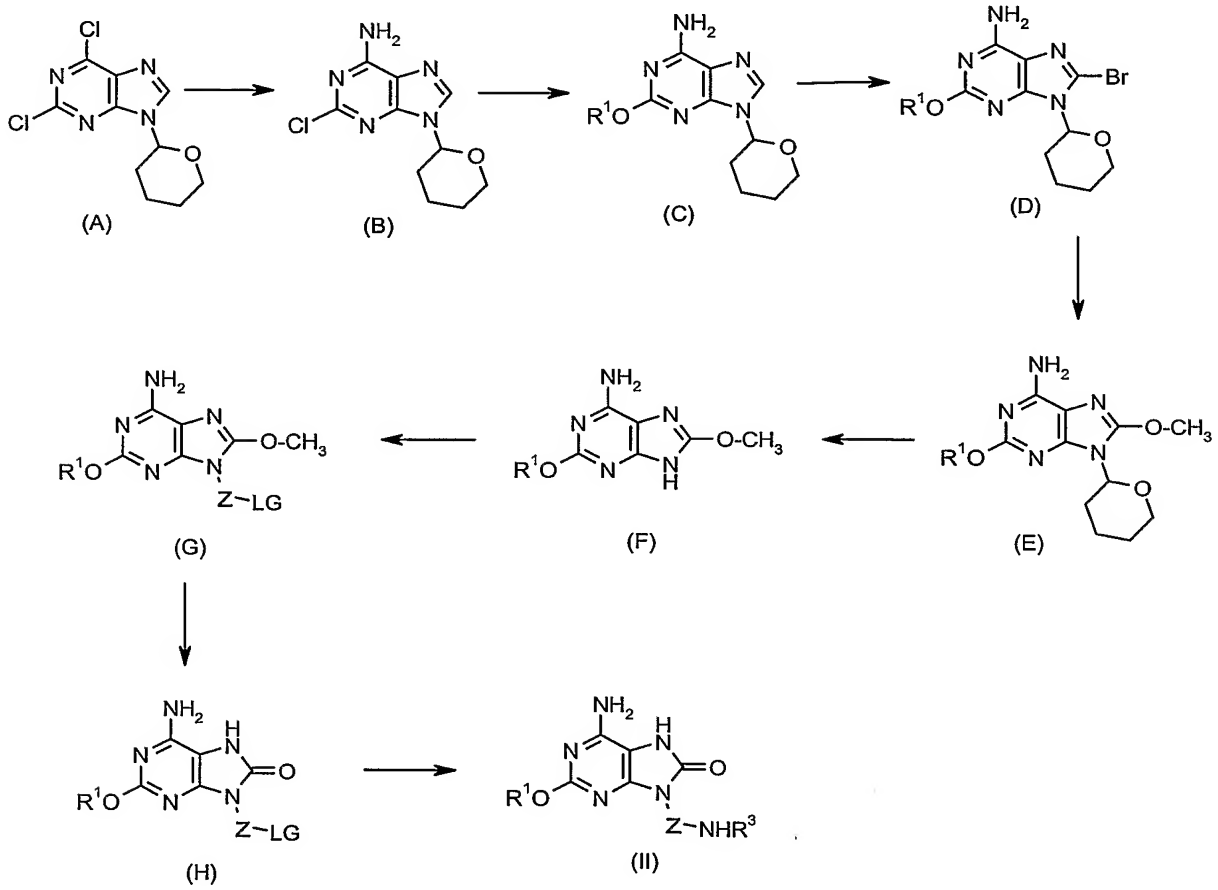
In process (b), the reaction may conveniently be carried out in an organic solvent such as acetonitrile, 1-methyl-2-pyrrolidinone or *N*,*N*-dimethylformamide at a temperature, for example, in the range from 0 to 150°C.

In process (c), the reaction may conveniently be carried out in an organic solvent such as acetonitrile, 1-methyl-2-pyrrolidinone or *N*,*N*-dimethylformamide at a temperature, for example, in the range from 0 to 150°C.

In process (d), the reaction may conveniently be carried out in an organic solvent such as 1-methyl-2-pyrrolidinone or *N*,*N*-dimethylformamide at a temperature, for example, in the range from 0 to 150°C.

In process (e), the reaction may conveniently be carried out in an organic solvent such as 1-methyl-2-pyrrolidinone, 1,2-dichloroethane or tetrahydrofuran at a temperature, for example, in the range from 0 to 150°C.

Compounds of formula (II) may be prepared as illustrated in the following reaction scheme:



The compound of formula (B) is prepared by reacting the compound of formula (A) with ammonia in an organic solvent such as methanol, ethanol, propanol, butanol, tetrahydrofuran, 1,4-dioxane, diglyme, acetonitrile or an aqueous mixture of any one of the preceding solvents. The reaction may be carried out in an autoclave, and at a temperature, for example, in the range from 20 to 200°C.

Compounds of formula (C) may be prepared by reacting the compound of formula (B) with a C_1-C_6 alkanol in the presence of a base such as sodium hydride and in an organic solvent such as tetrahydrofuran, 1,4-dioxane, diglyme, *N,N*-dimethylformamide or dimethylsulfoxide, preferably at elevated temperature, e.g. at a temperature in the range from 20 to 150°C. Alternatively an alkali metal such as sodium may be dissolved in the

C_1-C_6 alkanol and then reacted with the compound of formula (B), preferably at elevated temperature, e.g. at a temperature in the range from 20 to 150°C.

Compounds of formula (D) are prepared by brominating a compound of formula (C). The reaction may be carried out using a brominating agent such as bromine, hydroperbromic acid or *N*-bromosuccinimide, in an organic solvent such as carbon tetrachloride, methylene chloride, dichloroethane, diethyl ether, acetic acid or carbon disulfide. The reaction temperature will generally be in the range from 0°C to the boiling point of the solvent.

Compounds of formula (E) are prepared by reacting a compound of formula (D) with sodium methoxide in an organic solvent such as methanol and at a temperature, for example, in the range from 20 to 150°C.

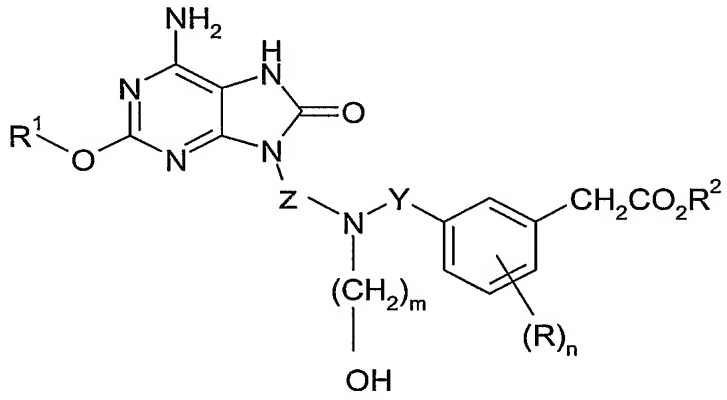
Compounds of formula (F) may be obtained by treating a compound of formula (E) with an acid such as trifluoroacetic acid in an organic solvent such as methanol.

Compounds of formula (G) are prepared by reacting a compound of formula (F) with a compound of formula LG-Z-LG wherein LG represents a leaving group such as a halogen, mesylate or triflate and Z represents a C_2-C_6 alkylene group as defined in formula (II). The reaction may be carried out in an organic solvent such as *N*,*N*-dimethylformamide, dimethylsulfoxide or acetonitrile with a base present, preferably at room temperature (20°C). A base such as an alkali metal carbonate, e.g. sodium carbonate or potassium carbonate; an alkaline earth metal carbonate, e.g. calcium carbonate; a metal hydroxide, e.g. sodium hydroxide or potassium hydroxide; a metal hydrogenate, e.g. sodium hydride; or a metal alkoxide, e.g. potassium t-butoxide, may be used.

Compounds of formula (H) may be obtained by treatment of a compound of formula (G) with an acid. The reaction may be carried out in an organic solvent such as methanol using either an inorganic acid such as hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as trifluoroacetic acid.

Compounds of formula (II) are prepared by reacting a compound of formula (H) with an amine of formula R^3NH_2 where R^3 is as defined in formula (II). The reaction may be carried out in an organic solvent such as acetonitrile or *N,N*-dimethylformamide using an excess of the amine, preferably at elevated temperature, e.g. at a temperature in the range from 0 to 150°C.

Compounds of formula (V) may be prepared by reacting a compound of formula

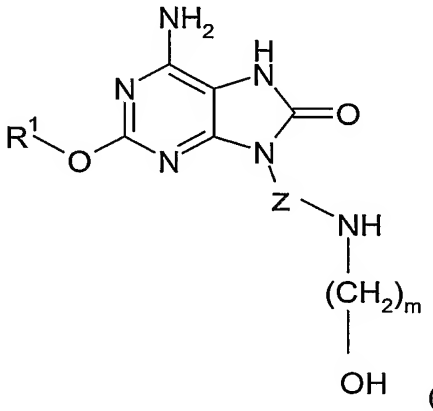


(X)

wherein m, n, Y, Z, R, R^1 and R^2 are as defined in formula (V) using standard procedures.

For example, compounds of formula (V) in which L^2 represents halogen, e.g. chlorine, may be prepared by reaction with a halogenating reagent such as thionyl chloride in an organic solvent such as dichloromethane at room temperature (20°C).

Compounds of formula (X) may be prepared by reacting a compound of formula

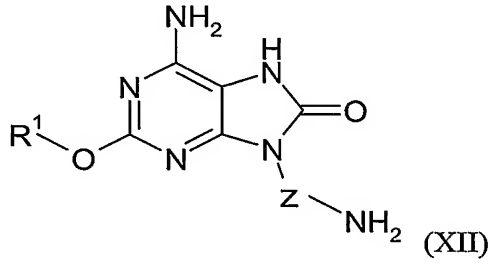


(XI)

wherein m, Z and R^1 are as defined in formula (x), with a compound of formula (III) or (IV) as defined above and under the same conditions as described in processes (a) and (b) respectively.

Compounds of formula (XI) may be prepared by reacting a compound of formula (H) as defined above with a C_2-C_6 aminoalcohol in an organic solvent such as acetonitrile or *N,N*-dimethylformamide using an excess of the aminoalcohol, preferably at elevated temperature, e.g. at a temperature in the range from 20 to 150°C.

Compounds of formula (VII) may be prepared by processes analogous to those described for the preparation of compounds of formula (X) using a compound of formula



(XII)

wherein Z and R^1 are as defined in formula (VII).

Compounds of formula (XII) may be obtained by reacting a compound of formula (F) as defined above with a compound of formula (XIII), L^4-Z-NH – P, wherein L^4 represents a leaving group (e.g. halogen, mesylate or triflate), P represents a nitrogen-protecting group (e.g. butoxycarbonyl) and Z is as defined in formula (XII), followed by removal of the nitrogen-protecting group, P, and removal of the oxygen-protecting group in the substituent $-OCH_3$.

The reaction between the compounds of formula (F) and (XIII) may be carried out in an organic solvent such as *N,N*-dimethylformamide, dimethylsulfoxide or acetonitrile with a base present, at a temperature, for example, in the range from 0 to 150°C. The base used may be an alkali metal carbonate, e.g. sodium carbonate or potassium carbonate; an alkaline earth metal carbonate, e.g. calcium carbonate; a metal hydroxide, e.g. sodium

hydroxide or potassium hydroxide; a metal hydrogenate, e.g. sodium hydride; or a metal alkoxide, e.g. potassium *tert*-butoxide. The removal of the protecting groups may be carried out according to methods known in the art.

Compounds of formulae (III), (IV), (VI), (VIII), (IX) and (XIII) are either commercially available, are known in the literature or may be prepared using known techniques.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example a compound of formula (I) where R^2 = methyl can be converted to a compound of formula (I) where R^2 = ethyl by treatment with a solution of hydrogen chloride in ethanol, at a temperature, for example in the range from 20 to 78°C.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including

racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of toll-like receptor (especially TLR7) activity, and thus may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In particular, the compounds of the invention may be used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis.

The invention still further provides a method of treating, or reducing the risk of, an obstructive airways disease or condition (e.g. asthma or COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the

range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention (including pharmaceutically acceptable salts) may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 micrometres (μm), and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium

stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as tumour necrosis factor alpha (TNF-alpha) inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin

molecules (such as Enbrel); non-selective cyclo-oxygenase COX-1/COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); glucocorticosteroids (whether administered by topical,oral, intramuscular, intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the invention and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention and a receptor antagonist for leukotrienes (LT B4, LTC4, LTD4, and LTE4) selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention and a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol.

The present invention further relates to the combination of a compound of the invention and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention and a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or inhibitors, including agents which act on cytokine signalling pathways.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

The present invention further relates to the combination of a compound of the invention and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention further relates to the combination of a compound of the invention together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

A compound of the invention can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:
(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);
(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase

inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin αvβ3 function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or

(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected

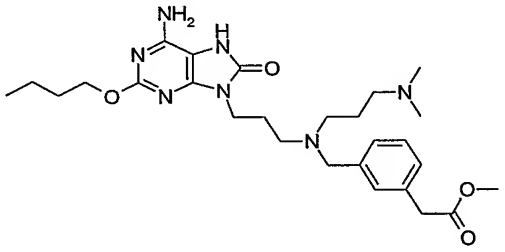
immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The present invention will be further explained by reference to the following illustrative examples.

Unless otherwise stated organic solutions were dried over magnesium sulphate. RPHPLC denotes Reversed Phase preparative High Performance Liquid Chromatography using Waters Symmetry C8, Xterra or Phenomenex Gemini columns using acetonitrile and either aqueous ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel. SCX denotes solid phase extraction with a sulfonic acid sorbent whereby a mixture was absorbed on a sulfonic acid sorbent and eluted with an appropriate solvent such as methanol or acetonitrile and then the free base product was eluted with aqueous ammonia/methanol or acetonitrile.

Example 1

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(dimethylamino)propyl]amino}methyl)phenyl]acetate



(i) 2-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purin-6-amine

2,6-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purine (55g) was dissolved in 7N-aqueous ammonia in methanol (500ml) and heated at 100°C in a sealed flask for 6 hours. The reaction mixture was cooled to room temperature and left overnight. Filtration afforded the subtitle compound. Yield 40g.

^{1}H NMR δ ($CDCl_3$) 8.02 (1H, s), 5.94 (2H, brs), 5.71 (1H, dd), 4.15 - 4.22 (1H, m), 3.75 - 3.82 (1H, m), 1.27 - 2.12 (6H, m).

(ii) 2-Butoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine

The product from step (i) (40g) was dissolved in 19%(w/w)-sodium butoxide in butanol (250ml). The reaction mixture was stirred under reflux for 6 hours. The resultant suspension was cooled to room temperature, diluted with water (250ml) and extracted with diethyl ether (200ml x 3). The combined organic phase was washed with water (200ml x 3), dried and concentrated *in vacuo*. The subtitle compound was crystallised from diethyl ether/isohexane (1/1, 300ml) and obtained by filtration. Yield 19g.

^{1}H NMR δ ($CDCl_3$) 7.87 (1H, s), 5.56 - 5.68 (3H, m), 4.31 - 4.35 (2H, t), 4.14 - 4.17 (1H, m), 3.76 - 3.80 (1H, m), 1.49 - 2.08 (10H, m), 0.98 (3H, t).

(iii) 8-Bromo-2-butoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

The product from step (ii) (30g) was dissolved in dry dichloromethane (200ml). The solution was stirred at room temperature whilst *N*-bromosuccinamide (27g) was added portionwise. The mixture was stirred at ambient temperature overnight. 20%(w/v)-Sodium sulfate (200ml) was added and the separated aqueous phase extracted with dichloromethane (200ml x 3). The combined organic phase was washed with saturated sodium hydrogen carbonate solution (200ml x 2) and brine (200ml). After concentration *in vacuo*, the residue was dissolved in ethyl acetate (300ml), washed with water (200ml), brine (200ml) and dried. The solution was filtered through silica gel and concentrated *in vacuo*. The residue was triturated with diethyl ether and isohexane (1/1, 200ml) then filtered to give the subtitle compound (26g). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (ethyl acetate/isohexane) to give a further 2.5g of product. The solids were combined to give the subtitle compound as a yellow solid. Yield 28.5g. Melting point: 148-150°C

^{1}H NMR δ ($CDCl_3$) 5.59-5.64 (3H, m), 4.32 (2H, m), 4.17 (1H, m), 3.74 (1H, m), 3.08 (1H, m), 2.13 (1H, d), 1.48 - 1.83 (8H, m), 0.98 (3H, t).

(iv) 2-Butoxy-8-methoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

Sodium (3.7g) was added to absolute methanol (400ml) under a nitrogen atmosphere. To this solution was added the product from step (iii) (28.5g) and the mixture was stirred at 65°C for 9 hours. The mixture was concentrated *in vacuo* and 500ml of water added. The aqueous phase was extracted with ethyl acetate (300ml x 2), washed with brine (200ml x 3) and dried. The subtitle compound was obtained after crystallisation from diethyl ether. Yield 14.2g.

^{1}H NMR δ ($CDCl_3$) 5.51(1H, dd), 5.28 (2H, brs), 4.29 (2H, t), 4.11 - 4.14 (4H, m), 3.70 (1H, m), 2.76 - 2.80 (1H, m), 2.05 (1H, d), 1.47 - 1.81 (8H, m), 0.97 (3H, t).

(v) 2-Butoxy-8-methoxy-9*H*-purin-6-amine, trifluoroacetate salt

The product from step (iv) (24g) was dissolved in absolute methanol (300ml) and 30ml of trifluoroacetic acid was added. The reaction mixture was stirred at ambient temperature for 3 days and concentrated *in vacuo*. The subtitle compound was obtained as a white crystalline solid after trituration with methanol/ethyl acetate. Yield 21g.

^{1}H NMR δ (CD_3OD) 4.48 (2H, t), 4.15 (3H, s), 1.80 (2H, quintet), 1.50 (2H, sextet), 0.99 (3H, t).

(vi) 9-(3-Bromopropyl)-2-butoxy-8-methoxy-9*H*-purin-6-amine

The product of step (v) (20g) was added in portions over 10 minutes to a rapidly stirred mixture of potassium carbonate (40g) and 1,3-dibromopropane (34ml) in *N,N*-dimethylformamide (250ml) at ambient temperature and the mixture stirred for 1.5 hours. The mixture was diluted with water (800ml) and extracted with ethyl acetate (300ml x 3). The combined extracts were washed with brine (200ml) and dried. The mixture was purified by column chromatography (ethyl acetate), to afford the subtitle compound as a white solid. Yield 16g.

^{1}H NMR δ ($CDCl_3$) 5.19 (2H, s), 4.28 (2H, J = 6.7 Hz, t), 4.12 (3H, s), 4.09 (2H, J = 9.4 Hz, t), 3.37 (2H, J = 13.3Hz, t), 2.39 - 2.30 (2H, m), 1.81 - 1.72 (2H, m), 1.55 - 1.43 (2H, m), 0.96 (3H, J = 11.4 Hz, t).

(vii) 6-Amino-9-(3-bromopropyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

The product of step (vi) (35.8g) was dissolved in methanol (400ml) and treated with 4M hydrogen chloride in dioxane (100ml). The mixture was stirred at ambient temperature for 6 hours and concentrated in *vacuo*. Dichloromethane (500ml) was added and concentrated *in vacuo*, which afforded a foam that was taken onto the next step without further purification. Yield 38g.

^{1}H NMR δ (DMSO-d_6) 10.60 (1H, s), 4.45 (2H, m), 3.84 (2H, m), 3.65 (2H, m), 2.19 (2H, m), 1.66 - 1.73 (2H, m), 1.36 - 1.47 (2H, m), 0.96 (3H, m).

(viii) 6-Amino-2-butoxy-9-{3-[(3-hydroxypropyl)amino]propyl}-7,9-dihydro-8*H*-purin-8-one

The product of step (vii) (6g) was suspended in acetonitrile (100ml) and 3-aminopropan-1-ol (20ml) was added. The mixture was stirred under reflux overnight. After cooling to room temperature, the mixture was concentrated *in vacuo* and 20%(w/v)-aqueous sodium hydrogen carbonate was added (100ml). The suspension was stirred at ambient temperature overnight, the solid collected via filtration, stored under high vacuum for 16 hours and dried to give the subtitle compound as a white solid. Yield 4.75g.

^{1}H NMR δ (DMSO-d_6) 6.40 (2H, brs), 4.15 (2H, J = 6.6 Hz, t), 3.70 (2H, J = 6.9 Hz, t), 3.44 (2H, m), 2.60 - 2.27 (4H, m), 1.77 - 1.23 (8H, m), 0.92 (3H, J = 7.5 Hz, t).
MS: APCI (+ve): 339 (M+H)

(ix) Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-hydroxypropyl)amino]methyl}phenyl)acetate

The product of step (viii) (4.75g) was dissolved in *N,N*-dimethylformamide (40ml). Potassium carbonate (2.00g) and methyl [3-(bromomethyl)phenyl]acetate (3.56g) were added. The mixture was stirred at ambient temperature overnight. 20%(w/v) aqueous sodium hydrogen carbonate was added (20ml) and the suspension stirred at ambient temperature overnight. The solid was collected via filtration, dried under high vacuum for 16 hours to give the subtitle compound as a white solid. Yield 4.91g.

^{1}H NMR δ (DMSO-d_6) 7.25 - 7.09 (4H, m), 6.39 (2H, brs), 4.33 (1H, J = 4.8 Hz, t), 4.12 (2H, J = 6.6 Hz, t), 3.66 (2H, J = 7.2 Hz, t), 3.64 (2H, s), 3.60 (3H, s), 3.50 (2H, s), 3.42 - 3.65 (2H, m), 2.44 - 2.27 (4H, m), 1.83 - 1.31 (8H, m), 0.90 (3H, J = 7.2 Hz, t).
MS: APCI (+ve): 501 (M+H)

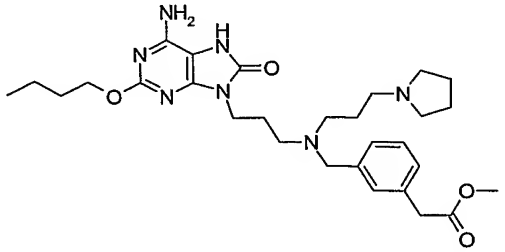
(x) Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(dimethylamino)propyl]amino}methyl)phenyl]acetate

The product of step (ix) (200mg) was suspended in dichloromethane (3ml) and thionyl chloride (0.06ml) added. The solution was stirred at ambient temperature for 5 hours and concentrated *in vacuo* azeotropically with toluene (100ml). Sodium iodide (200mg) and 2M solution of *N,N*-dimethylamine (4ml) in tetrahydrofuran were added. The mixture was heated at 50°C for 72 hours in a sealed tube. After cooling to ambient temperature, the mixture was treated with SCX and purified by RPHPLC, to afford the title compound as a white solid. Yield 96mg.

^{1}H NMR δ (DMSO-d_6) 7.25 - 7.08 (4H, m), 6.52 (2H, brs), 4.11 (1H, J = 6.6 Hz, t), 3.66 (2H, J = 6.9 Hz, t), 3.63 (2H, s), 3.59 (3H, s), 3.49 (2H, s), 2.43 - 2.32 (4H, m), 2.12 (2H, J = 6.9 Hz, t), 2.03 (6H, s), 1.66 - 1.30 (8H, m), 0.90 (3H, J = 7.2 Hz, t).
MS: APCI (+ve): 528 (M+H)

Example 2

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-pyrrolidin-1-ylpropyl)amino]methyl}phenyl)acetate

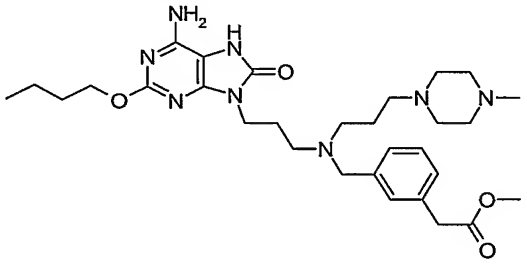


The title compound was prepared by a method analogous to that described in Example 1 above using pyrrolidine. Yield 150mg.

^{1}H NMR δ (DMSO-d_6) 7.25 - 7.09 (4H, m), 6.37 (2H, brs), 4.12 (1H, J = 6.6 Hz, t), 3.66 (2H, J = 7.2 Hz, t), 3.64 (2H, s), 3.59 (3H, s), 3.49 (2H, s), 3.31 - 2.72 (2H, m), 2.72 - 2.29 (10H, m), 1.82 - 1.23 (10H, m), 0.90 (3H, J = 7.2 Hz, t).
MS: APCI (+ve): 554(M+H)

Example 3

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate

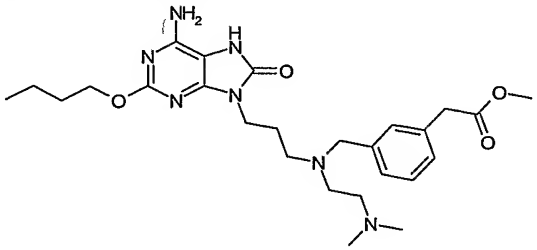


The title compound was prepared by a method analogous to that described in Example 1 above using *N*-methylpiperazine. Yield 50mg.

^{1}H NMR δ (DMSO-d_6) 7.24 - 7.09 (4H, m), 6.45 (2H, brs), 4.11 (1H, J = 6.4 Hz, t), 3.66 (2H, J = 7.2 Hz, t), 3.63 (2H, s), 3.59 (3H, s), 3.48 (2H, s), 3.31 (2H, m), 2.49 - 2.16 (12H, m), 2.10 (3H, s), 1.83 - 1.24 (8H, m), 0.90 (3H, J = 7.2 Hz, t).
MS: APCI (+ve): 583(M+H)

Example 4

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][2-(dimethylamino)ethyl]amino}methyl)phenyl]acetate



(i) 6-Amino-2-butoxy-9-(3-{[2-(dimethylamino)ethyl]amino}propyl)-7,9-dihydro-*8H*-purin-8-one

The subtitle compound was prepared by a method analogous to that of Example 1 step (viii) using *N,N*-dimethylethane-1,2-diamine. Yield 0.5g.

MS: APCI (+ve): 352 (M+1)

(ii) Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][2-(dimethylamino)ethyl]amino}methyl)phenyl]acetate

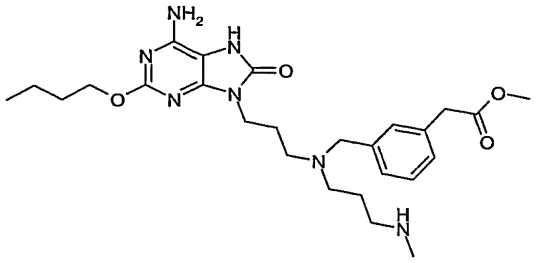
The product from step (i) (500mg) was dissolved in a mixture of 1,2-dichloroethane (12ml) and 1-methyl-2-pyrrolidinone (3ml). (3-Formyl-phenyl)-acetic acid methyl ester (300mg) and sodium triacetoxyborohydride (425mg) were added and the mixture stirred at ambient temperature for 4 hours. After removing the solvent, the residue was partitioned between dichloromethane (100ml) and saturated aqueous sodium hydrogen carbonate (100ml), the organic layer dried and concentrated *in vacuo*. The residue was purified by RPHPLC to afford the title compound. Yield 260mg.

^{1}H NMR δ (DMSO-d_6) 9.82 (1H, s), 7.24 - 7.16 (3H, m), 7.10 (1H, d), 6.38 (2H, s), 4.12 (2H, t), 3.68 (2H, t), 3.64 (2H, s), 3.59 (3H, s), 3.52 (2H, s), 2.45 - 2.41 (4H, m), 2.27 - 2.23 (2H, m), 2.04 (6H, s), 1.85 - 1.80 (2H, m), 1.65 - 1.58 (2H, m), 1.39 - 1.33 (2H, m), 0.90 (3H, t).

MS: APCI (+ve): 514

Example 5

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylamino)propyl]amino}methyl)phenyl]acetate



(i) *tert*-Butyl (3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}propyl)methylcarbamate

The subtitle compound was prepared by a method analogous to that of Example 1 step (viii) using *tert*-butyl (3-aminopropyl)methylcarbamate. Yield 430mg.

MS: APCI (+ve): 452

(ii) Methyl {3-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl] {3[(*tert*-butoxycarbonyl)(methyl)amino]propyl}amino)methyl] phenyl} acetate

The subtitle compound was prepared by a method analogous to that of Example 1 step (ix) using the product of step (i). The subtitle compound obtained (200mg) was taken onto the next step without further purification.

MS: APCI (+ve): 614

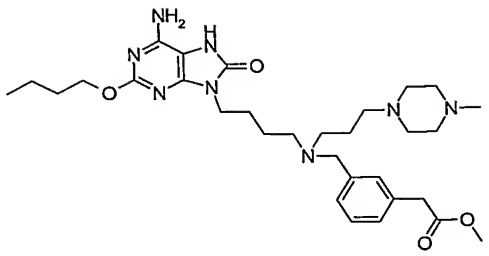
(iii) Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylamino)propyl]amino}methyl)phenyl]acetate

The product from step (ii) (200mg) was dissolved in methanol (5ml) and 4M hydrogen chloride in dioxane (5ml) added. The mixture was stirred at room temperature for 72 hours and concentrated *in vacuo*. The mixture was purified by RPHPLC, to afford the title compound as a white solid. Yield 35mg.

^{1}H NMR δ (DMSO-d_6) 7.24 - 7.15 (3H, m), 7.10 (1H, d), 6.40 (2H, s), 4.12 (2H, t), 3.67 (2H, t), 3.64 (2H, s), 3.59 (3H, s), 3.48 (2H, s), 2.42 - 2.36 (6H, m), 2.20 (3H, s), 1.85 - 1.78 (2H, m), 1.65 - 1.58 (2H, m), 1.54 - 1.47 (2H, m), 1.41 - 1.31 (2H, m), 0.90 (3H, t).
MS: APCI (+ve): 514

Example 6

Methyl [3-({[4-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)butyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate



(i) 9-(3-Bromopropyl)-2-butoxy-8-methoxy-9*H*-purin-6-amine

The subtitle compound was prepared by a method analogous to that of Example 1 step (vi) using 1,4-dibromobutane. Yield 16g.

MS: APCI (+ve): 373/375 = 1/1 (M+H) bromide isotope pattern

(ii) 3-{[4-(6-Amino-2-butoxy-8-methoxy-9*H*-purin-9-yl)butyl]amino}propan-1-ol

The subtitle compound was prepared by a method analogous to that of Example 1 step (viii) using the product of step (i). Yield 6g.

MS: APCI (+ve): 339 (M+H)

(iii) Methyl (3-{[[4-(6-amino-2-butoxy-8-methoxy-9*H*-purin-9-yl)butyl](3-hydroxypropyl)amino]methyl}phenyl)acetate

The subtitle compound was prepared by a method analogous to that of Example 1 step (ix) using the product of step (ii). Yield 6g.

MS: APCI (+ve): 529 (M+H)

(iv) Methyl (3-{[[4-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)butyl](3-hydroxypropyl)amino]methyl}phenyl)acetate

The title compound was prepared by a method analogous to that of Example 1 step (vii) using the product of step (iii). Yield 10g.

MS: APCI (+ve): 515 (M+H)

(v) Methyl [3-({[4-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)butyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate

The title compound was prepared by a method analogous to that of Example 1 step (x) using the product of step (iv). Yield 200mg.

^{1}H NMR δ (DMSO-d_6) 9.81 (1H, s), 7.27 - 7.03 (4H, m), 6.38 (2H, s), 4.18 - 4.08 (2H, m), 3.65 - 3.60 (4H, m), 3.58 (3H, s), 3.48 - 3.40 (2H, m), 3.37 - 3.26 (4H, m), 2.39 - 2.27 (4H, m), 2.27 - 2.19 (4H, m), 2.20 - 2.14 (2H, m), 2.10 (3H, s), 1.69 - 1.57 (4H, m), 1.55 - 1.43 (2H, m), 1.44 - 1.32 (4H, m), 0.91 (3H, t).

MS: APCI (+ve): 597 (M+H)

Biological Assays

(1) Interferon-inducing activity of rat spleen cells (in vitro)

Spleens were removed from male Sprague-Dawley rats (approximately 8-10 weeks old) and a splenocyte suspension was prepared in serum-free MEM medium (modified Eagle's medium). Test compounds were dissolved in dimethylsulfoxide (DMSO), and incubated with splenocytes (5×10^6 cells/ml) keeping the final DMSO concentration at 0.1%. Incubations were for 24 hours at 37°C under an atmosphere of 5% carbon dioxide (CO_2) at which point supernatants were collected and analyzed for interferon *alpha* (IFNα). IFNα levels were determined in a bioassay by measuring the IFNα-mediated inhibition of vesicular stomatitis virus-induced cellular death of L929 cells. Values quoted are for the log of the minimum effective concentration (MEC) of test compound required to induce IFNα.

Example No.	**1**	**2**	**3**	**4**	**5**	**6**
Log MEC	9.5	9.5	9.5	9.5	9.5	9.0

(2) Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was

maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the minimal effective concentration of compound to induce SEAP release (pMEC).

Compound of Example 2:	pMEC 7.4
Compound of Example 3:	pMEC 7.7
Compound of Example 5:	pMEC 7.2.

Solubility Testing

Saturated solutions for determining the solubility were prepared by placing about 0.3 - 3.0 ml of 0.1M phosphare buffer in glass screw-top sample tubes along with some of the test compound. The tubes were then shaken overnight at constant temperature (20°C). After shaking, undissolved material should be present in the solution, and more test compound should be added and shaking continued if this is not the case. The samples were then transferred to a centrifuge tube and centrifuged using a Heraeus Biofuge Fresco centrifuge at 13000 rpm for 30 minutes. The supernatant was then removed, placed in a new centrifuge tube and centrifuged again for 30 minutes at 13000 rpm. The undissolved material formed a pellet at the bottom of the tube and the liquid above the pellet was removed and was ready for assaying. The solution was then analysed using HPLC with UV quantification. A standard was also prepared by accurately weighing a sample of the test compound and dissolving it in a suitable volume of a solvent that will dissolve it

completely (typically, DMSO, ethanol or methanol). This sample was then analysed by HPLC/UV.

Results

The solubility was calculated from the observed peak areas in the HPLC/UV chromatograms along with corrections for any dilutions of the sample and differences in injection volumes. The following equation was used:

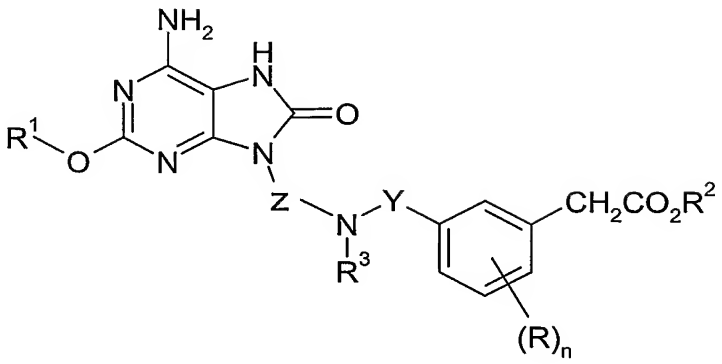
$$\text{Solubility (mg/ml)} = \left(\frac{\text{Std Conc (mg/ml)} . \text{Sample Peak Area} . \text{Sample Dilution factor} . \text{Std Inj Vol}}{\text{Std Peak Area} . \text{Sample Inj Vol}} \right)$$

Example	**1**	**2**	**3**	**4**	**5**	**6**
Solubility (mg/ml)	0.98	1.94	0.85	0.83	1.82	1.21

Comparison Examples from PCT/JP2005/005401	**2-13**	**2-31**	**2-35**
Solubility (mg/ml)	0.05	0.02	0.16

CLAIMS

1. A compound of formula



(I)

wherein

R^1 represents a C_1-C_6 alkyl group;

Z represents a C_2-C_6 alkylene group;

Y represents a C_1-C_3 alkylene group;

R^2 represents a C_1-C_6 alkyl group;

n is an integer from 0 to 2;

each group R independently represents halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy or C_1-C_3 haloalkyl;

R^3 represents $-(CH_2)_m$-NR^4R^5;

m is an integer from 2 to 6;

either R^4 and R^5 each independently represent hydrogen or C_1-C_6 alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring optionally comprising a further ring hetero group NR^6; and

R^6 represents hydrogen or C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 represents a C_1-C_4 alkyl group.

3. A compound according to claim 1 or claim 2, wherein Z represents a C_2-C_4 alkylene group.

4. A compound according to any one of claims 1 to 3, wherein Y represents methylene.

5. A compound according to any one of the preceding claims, wherein R^4 and R^5 each independently represent hydrogen or C_1-C_3 alkyl.

6. A compound according to any one of claims 1 to 4, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring optionally comprising a further ring hetero group NR^6.

7. A compound according to any one of the preceding claims, wherein R^2 represents a C_1-C_3 alkyl group.

8. A compound according to claim 1 wherein

R^1 represents n-butyl;

Z represents n-propylene or n-butylene;

Y represents methylene;

R^2 represents methyl;

n is 0;

R^3 represents $-(CH_2)_m$-NR^4R^5;

m is 2 or 3;

either R^4 and R^5 each independently represent hydrogen or methyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 5- to 6-membered saturated heterocyclic ring optionally comprising a further ring hetero group NR^6; and

R^6 represents methyl.

9. A compound according to claim 1 selected from:

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(dimethylamino)propyl]amino}methyl)phenyl]acetate,

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](3-pyrrolidin-1-ylpropyl)amino]methyl}phenyl)acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][2-(dimethylamino)ethyl]amino}methyl)phenyl]acetate,

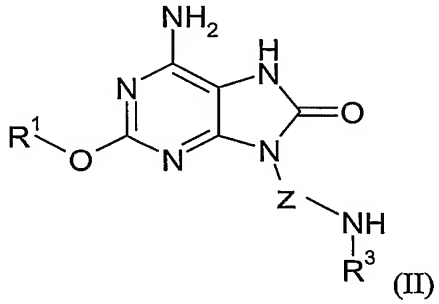
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylamino)propyl]amino}methyl)phenyl]acetate,

Methyl [3-({[4-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)butyl][3-(4-methylpiperazin-1-yl)propyl]amino}methyl)phenyl]acetate,

and pharmaceutically acceptable salts of any one thereof.

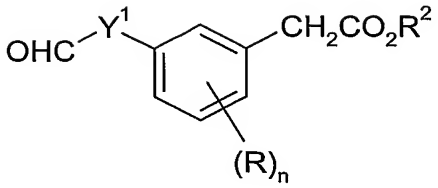
10. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula



(II)

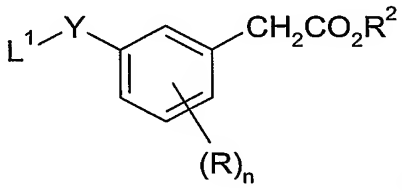
wherein Z, R^1 and R^3 are as defined in formula (I), with a compound of formula



(III)

wherein Y^1 represents a bond or C_1-C_2 alkylene group and n, R and R^2 are as defined in formula (I) in the presence of a suitable reducing agent; or

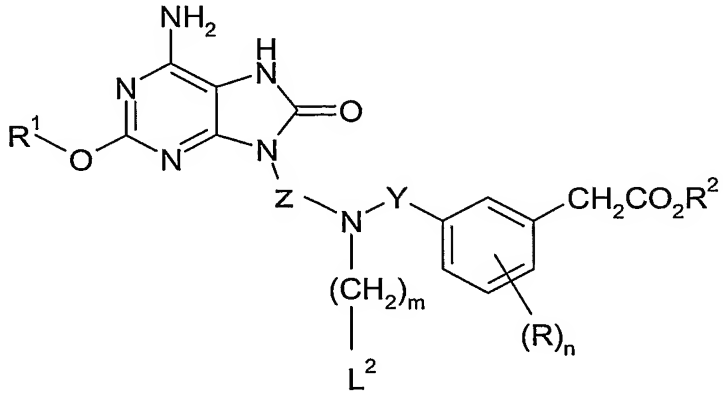
(b) reacting a compound of formula (II) as defined in (a) above with a compound of formula



(IV)

wherein L^1 represents a leaving group and n, Y, R and R^2 are as defined in formula (I) in the presence of a suitable base; or

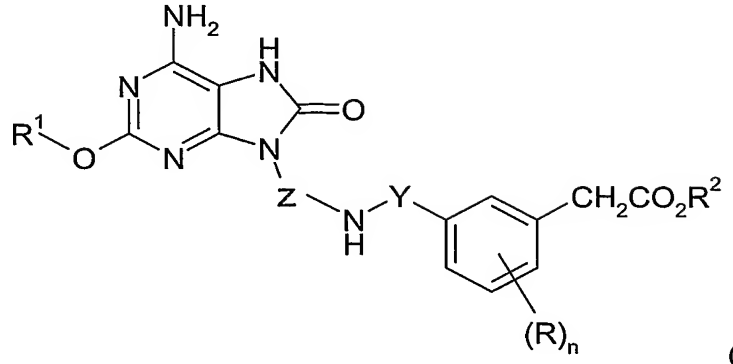
(c) reacting a compound of formula



(V)

wherein L^2 represents a leaving group and m, n, Y, Z, R, R^1 and R^2 are as defined in formula (I), with a compound of formula (VI), HNR^4R^5, wherein R^4 and R^5 are as defined in formula (I); or

(d) reacting a compound of formula



(VII)

wherein n, Y, Z, R, R^1 and R^2 are as defined in formula (I), with a compound of formula

$$L^3\text{-}(CH_2)_m\text{-}NR^4R^5 \quad \text{(VIII)}$$

wherein L^3 represents a leaving group and m, R^4 and R^5 are as defined in formula (I); or

(e) reacting a compound of formula (VII) as defined in (d) above with a compound of formula

$$OHC\text{-}(CH_2)_{m-1}\text{-}NR^4R^5 \quad \text{(IX)}$$

wherein m, R^4 and R^5 are as defined in formula (I) in the presence of a suitable reducing agent;

and optionally after (a), (b), (c), (d) or (e) carrying out one or more of the following:

- converting the compound obtained to a further compound of formula (I)
- forming a pharmaceutically acceptable salt of the compound.

11. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable

salt thereof as claimed in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I) or a pharmaceutically-acceptable salt thereof as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of TLR7 activity is beneficial.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for the treatment of allergic or viral diseases or cancers.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in treating asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, bacterial infections and dermatosis.

17. A method of treating, or reducing the risk of, a disease or condition in which modulation of TLR7 activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9.

18. A method of treating, or reducing the risk of, an allergic or viral disease or cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9.

19. A method of treating, or reducing the risk of, an obstructive airways disease or condition which comprises administering to a patient in need thereof a therapeutically

effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003364

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D473/18 A61K31/522 A61P31/12 A61P35/00 A61P37/02 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/092893 A (SUMITOMO PHARMA [JP]; ASTRAZENECA AKTIEBOLAG [SE]; KURIMOTO AYUMU [JP]) 6 October 2005 (2005-10-06) cited in the application abstract page 94; examples pages 116-122; examples claims	1-19
A	EP 1 035 123 A1 (SUMITOMO PHARMA [JP]; JAPAN ENERGY CORP [JP] SUMITOMO PHARMA [JP]) 13 September 2000 (2000-09-13) cited in the application abstract examples claims	1-19

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2006	07/11/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stix-Malaun, Elke

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003364

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/04449 A2 (NEOTHERAPEUTICS INC [US]; TAYLOR EVE M [US]) 17 January 2002 (2002-01-17) abstract examples claims	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/003364

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/003364

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005092893 A	06-10-2005	AU 2005226359 A1	06-10-2005
EP 1035123 A1	13-09-2000	AT 247654 T	15-09-2003
		AU 732361 B2	26-04-2001
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